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Smoking and Lung Cancer: Risk as a Function of Cigarette Tar Content[1]

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The hypothesis of reduction in lung cancer risk associated with the adoption of low-tar cigarettes was examined in a subset of subjects from a population-based, case-control study of incident primary lung cancer among New Jersey white men. Risk was related to time-weighted average tar levels of cigarettes smoked in 1973-1980. Unadjusted estimates of risk were significantly low for the lowest tar (<14 mg cig) smokers [odds ratio = 0.53 (0.29,0.97)] compared with the highest (21.1-28 mg/cig). However, adjustment by age and total pack-years rendered the risk reduction insignificant. Of note was the finding that cases who smoked low-tar cigarettes compensated for reducing tar by *increasing* the number of cigarettes they smoked by almost half a pack per day from the years 1963-1972 to 1973-1980, while in the same period controls and high-tar cigarette smoking cases did not increase the numbers smoked.

INTRODUCTION

Cigarette smoking is generally recognized as the primary cause of lung cancer (23-25). Tar, the total dry particulate component of smoke, is a complex mixture of hundreds of substances. There is a body of information classifying these tar compounds as initiators, promoters, cocarcinogens, and so on, and increased consensus as to how these molecules act (28, 31). As to the general conclusion that cigarette tar constituents increase cancer risk, there is no dispute (25).

The quantity of tar per average cigarette marketed in the United States has been declining steadily over three decades for two reasons. The mix of product purchased by the smoking public has shifted, first as filter cigarettes became prevalent in the 1950s, and subsequently as companies introduced new brands to compete for the perceived "low-tar" market. Also, tar reductions have occurred as manufacturers reformulated cigarette brands continuously available from before 1950 to the present. Before 1953, the average tar content of cigarettes was approximately 35 mg each. By 1962, tar in nonfilter cigarettes had declined to about 30 mg each and filters to 22 mg. After another decade, non-filters tested at 27 mg and filters at 17-18 mg. In 1980, non-filters averaged 24 mg and filters only 11 mg.

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Therefore, one might hypothesize some corresponding, measurable impact of this decreasing tar content on lung cancer incidence or risk. This may be phrased in one of two ways: (a) is there decreased lung cancer risk for persons who smoke low-tar cigarettes exclusively; and (b) is present smoking of lower-tar cigarettes, after some term of smoking higher-tar ones, associated with decreased lung cancer risk? We have investigated the latter using data from a population-based incident lung cancer case–control interview study of white men from six areas of New Jersey.

METHODS

All incident white male lung cancer cases diagnosed during the period of September 1980 to October 1981, and occurring in six previously noted high-mortality areas of New Jersey (21), were identified. Cases were ascertained via a rapid reporting system established between the New Jersey Department of Health and local hospital pathology departments, by regular review of hospital pathology logs, and by monitoring the State Cancer Registry and death certificate files. Health Department physicians reviewed pathology reports, along with supporting medical records as required, in order to verify a diagnosis of primary lung cancer. Only histologically confirmed cases were retained for study.

Population-based controls were selected using two procedures. Controls for directly interviewed cases were selected from a random sample of men with New Jersey motor vehicle licenses. This sample was frequency matched to cases by geographic area, race, and 5-year age group. Controls for deceased or incapacitated cases were selected from state death certificate files, and were individually matched to cases by area, race, age, and closest date of death (or date of death nearest the date of diagnosis, for incapacitated cases). Certificates indicating lung cancer or any other respiratory disease as an underlying or contributory cause of death were excluded.

Of the 1,084 white male lung cancer cases eligible for the study, interviews were successfully completed for 763 (70.4%), 429 with self-respondents and 334 with next-of-kin (308 first-degree relatives, 26 more distant). Reasons for noninclusion were late ascertainment (6.9%), insufficient time after death to allow the waiting period required by the Institutional Review Board before contacting next-of-kin (2.1%), physician refusal (4.2%), untraceable respondent (4.2%), respondent refusal (10.8%), and poor-quality interviews (1.4%). Of the 1,415 white male controls identified, interviews were successfully completed with 900 (63.6%), 564 with self-respondents and 336 with next-of-kin (318 first- degree relatives, 18 more distant). Reasons for noninclusion were untraceable respondent (9.0%), respondent refusal (24.7%), and poor-quality interviews (2.8%).

All interviews of subjects or their next-of-kin were conducted in person by field staff experienced in large-scale epidemiologic studies. The modular questionnaire included sections on demographic factors, residential history, personal and familial medical history, history of cigarette, pipe, and cigar smoking, smoking by other household members, occupational history (20), and dietary history (30).

In the cigarette use section of the questionnaire, a smoker first was asked to recall the years in which he smoked cigarettes for any period 6 months or longer.

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Second, he was asked to recall the brands of cigarettes he smoked during each period, the specific years in which he smoked each brand, the number of cigarettes of each brand smoked per day, and the depth of inhalation for each. The interviewer probed for any changes in number per day of a particular brand; a change greater than 10 per day generated a new data entry. The sequence of temporal episodes yielded the summary measures of age started smoking cigarettes, years actually smoked, and years since cessation (if any). The collection of brand name and intensity records for each episode yielded a lifetime intensity measure, or average number of cigarettes smoked per day. A total exposure measure, lifetime packyears, was calculated from the intensity and duration measures. The tar content per cigarette for any brand in any year was determined from historical estimates (22, 24) and test data (4, 5).

Time-weighted average tar levels were calculated for the interval 1973–1980. This period was selected because (a) precise figures for tar content of all domestically produced cigarettes are available; (b) except for the last years of the interval, 1979 and 1980, when ultra-low-tar cigarettes became available, this period did not show so sharp a decline in tar content as the two previous decades; and (c) this proximal portion of the smoking history was assumed to be recalled more accurately by both self- and next-of-kin respondents. We have included smokers with complete brand-specific smoking histories who smoked continuously throughout the interval 1973–1980. Smokers who had quit during the interval were excluded, as were those who stopped prior to 1973.

We compared frequencies of exposure to different 1973–1980 tar levels between cases and controls using the Mantel–Haenszel summary odds ratio (15) with test-based 95% confidence limits (16). Strength of trend was tested by Mantel's method (14), heterogeneity of the odds ratio among sample subgroups was estimated by the method of Breslow and Day (1), and significance of the difference of means by the t test (19). We adjusted for lifetime characteristics of smoking using intensity, duration, intensity and duration simultaneously, or packyears. We examined further possible confounding by respondent type, study area, age at diagnosis, level of education, ever/never smoked pipes and/or cigars, consumption of vegetables, and employment in high-risk occupations (20). We used multiple logistic regression models for simultaneous adjustment by packyears and other potential confounders (1, 18).

RESULTS

Of the 763 cases and 900 controls in the study sample, 13 cases and 142 controls never smoked any tobacco product and 727 cases and 671 controls smoked cigarettes for at least 6 months for an overall crude odds ratio of 11.8 (7.4, 18.9). The other tobacco users, 23 cases and 87 controls, smoked only pipes and/or cigars, and had a crude odds ratio of 2.89 (1.42, 5.88).

Restriction of the sample to those with complete smoking histories reduced the number of cigarette smokers from 1,398 (Table 1, All) to 1,142 (Table 1, subset A), but made little difference in the distribution of cases and controls by age and by summary smoking measures. Differences between cases and controls for the summary smoking measures were significant and similar in magnitude in the total

TABLE 1

CHARACTERISTICS OF CASE AND CONTROL CIGARETTE SMOKERS, WITH SUCCESSIVE RESTRICTIONS OF SAMPLE, NEW JERSEY WHITE MEN, 1980–1981[a]

	All cigarette smokers		Subset A: all with complete smoking histories		Subset B: all in A who smoked throughout 1973–1980	
	Cases	Controls	Cases	Controls	Cases	Controls
Number of subjects	727	671	583	559	373	247
Age, years	64.7	64.4	64.2	64.1	62.1	62.5
Intensity, cigarettes/day	29.3	24.7*	29.4	23.8*	29.8	23.8*
Duration, years	43.5	36.4*	42.6	35.7*	46.4	45.0
Smoking cessation, years	4.7	10.1*	5.0	10.5*	0.043	0.061
Age began smoking, years	16.5	17.6*	16.6	17.6*	15.7	16.9*
Total exposure, packyears	64.4	46.2*	63.0	43.7*	68.8	53.2*

[a] Mean value.

* $P < 0.05$ for difference between means of cases and controls.

sample and in the first subset; there were no case–control age differences. Further restricting the sample to those who smoked throughout the interval 1973–1980 (Table 1, subset B) reduced the mean number of years since cessation to nearly zero, and erased the previously noted case–control difference for duration. The remaining analyses refer only to these 620 subjects.

Due to the reduction in tar content of both non-filter and filter cigarettes, the average tar level of the cigarettes smoked during 1973–1980 did not exceed 28 mg, 80% of the pre-1953 level of 35 mg tar per cigarette. The median tar level for the 373 cases was 18.6 mg/cig and for the 247 controls was 18.2 mg/cig.

Four tar-level groups were selected. The frequency distribution of tar levels for controls showed three peaks, one consisting of the subjects smoking cigarettes with 21–28 mg tar, another consisting of the very-low-tar smokers, at 14 mg or less, and the bulk of the smokers in a broad middle group that we divided just above the modal value of 17.5 mg/cig. Table 2 shows that the unadjusted odds ratio for subjects at the lowest tar level, relative to subjects at the highest level, was significantly lower than 1.0. There was a significant trend (one-sided P = 0.04) in odds ratios with increasing tar. However, taking cognizance of the subject's lifetime smoking behavior increased the odds ratio for the lowest-tar group so that it was no longer significantly different from the reference level. Controlling for packyears resulted in the greatest shift of the odds ratio toward 1.0.

We examined possible differences in the packyear-adjusted tar-level odds ratios by respondent type. Although self-respondents showed a more consistent pattern in odds ratios with increasing tar, the trend was not significant; none of the odds ratios was significantly different from the reference level, and there was no significant heterogeneity by respondent type at any tar level. The packyear and respondent type-adjusted odds ratios were almost identical to those previously shown in Table 2 for adjustment by packyears alone.

We made similar comparisons of age-specific odds ratios, because the association with tar might be more pronounced in younger persons, with a shorter early

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TABLE 2

ODDS RATIOS FOR LUNG CANCER ASSOCIATED WITH TAR LE L OF CIGARETTES SMOKED IN 1973–1980, ADJUSTED BY OTHER LIFETIME MEASURES OF IGARETTE CONSUMPTION[a,b]

	Tar level, 197 1980, mg/cigarette			
	≤14.0	14.1–17.5	17.6–21.0	21.1–28.0[c]
Number of cases/controls:	25/28	131/91	78/45	139/83
Unadjusted odds ratio	0.53 (0.29,0.97)	0.86 (0.59,1.26)	1.04 (0.66,1.64)	1.00
Adjusted by intensity[d]	0.61 (0.33,1.12)	1.01 (0.68,1.51)	1.16 (0.72,1.86)	1.00
Adjusted by duration[e]	0.58 (0.32,1.07)	0.89 (0.60,1.32)	1.05 (0.65,1.67)	1.00
Adjusted by intensity and duration[f]	0.61 (0.32,1.13)	1.04 (0.70,1.56)	1.21 (0.75,1.96)	1.00
Adjusted by packyears[g]	0.71 (0.37,1.35)	1.06 (0.71,1.59)	1.19 (0.73,1.93)	1.00

[a] Sample includes smokers with complete smoking historie: vho smoked throughout 1973–1980 (subset B in Table 1).

[b] Mantel–Haenszel estimate of odds ratio (95% confidence li ts).

[c] Reference group.

[d] As <20 cig/day, 20–29, 30–39, 40–49, 50+.

[e] As <30 years, 30–39, 40–49, 50+.

[f] Intensity as for [d], duration <40 years, 40+.

[g] As <20 packyears, 20–39, 40–59, 60–79, 80–99, 100+.

history of smoking the available high-tar cigarett : There was little consistent variation by age; the youngest age quartile showed o pattern in risk with increasing tar. The packyear and age-adjusted odds ratios /ere again almost identical to those shown in Table 2, except that the odds rat for the lowest-tar group increased further to 0.85 (0.42, 1.75).

Because vegetable consumption is associated wi 1 lung cancer most strongly in current and recent ex-smokers (30), we were co erned that the effect of diet might mask an association with tar. Therefore w calculated packyear-adjusted odds ratios by tar level and vegetable consumpti n, relative to subjects in the highest-tar/lowest vegetable consumption group. he association with tar was apparent only in the group with highest vegetable nsumption, among whom the lowest-tar subgroup showed a significantly low od ratio of 0.24 (0.07, 0.83). The trend in odds ratios with increasing tar in this hi 1 vegetable group had a one-sided P value of 0.06. The result of adjustment l packyears and by vegetable consumption simultaneously was no different tha obtained from adjustment by packyears alone; there was little consistent overa association with tar. Furthermore, adjustment by tar level and packyears did n change the significant inverse association of lung cancer with vegetable consum tion (32).

Adjustment by other potential confounders, for xample degree of inhalation or education in addition to packyears, did not apprec bly change any of the patterns in odds ratios previously described. The same w true of the logistic regression analysis. Examination of different combinations factors suggested that signif-

icant contributors to the predictive power of the model were packyears, age, vegetable consumption, and employment in high-risk occupations. Inclusion of these resulted in odds ratios of 0.83 (0.43, 1.60), 1.11 (0.74, 1.67), 1.28 (0.78, 2.10), and 1 for the four tar levels.

It is possible that smokers, although receiving some unspecified amount of risk reduction by using lower-tar cigarettes, could negate that benefit by smoking more cigarettes. We compared, for cases and controls at each tar level, differences between the numbers of cigarettes smoked per day in the interval 1973–1980 and the intensity in the immediately preceding decade (Table 3). Overall, cases increased their consumption more than controls did, although this difference was not significant. Among cases, there was a consistent increase in intensity with decreasing tar, whereas among controls there was no consistent pattern. The difference between case and control changes in consumption was significant for the lowest-tar group. We further attempted to localize this difference to a particular tar level of cigarettes smoked in 1963–1972. The only significant difference in changes in numbers of cigarettes per day between cases and controls was that for smokers who were in the lowest-tar category in *both* 1963–1972 and 1973–1980. These 19 cases increased their consumption by 9.3 cigarettes per day between the two time periods, whereas the 13 controls showed no change whatever in consumption.

DISCUSSION

In addressing the question of whether smoking of low-tar cigarettes is associated with decreased lung cancer risk, the cardinal problem is one of definition: what is a low-tar cigarette? The way this problem has been approached by many is to differentiate cigarettes by a proxy variable, whether they are filtered or not (2, 12, 29, 30). While the amount of tar in filter cigarettes as a class probably has never been greater than that in nonfilter cigarettes, it should be noted that filter cigarettes initially available in the early 1950s had higher tar content than plain tip ones today; "high" and "low" are relative terms.

An alternative approach used by others (8, 10, 13, 26), and with which we

TABLE 3

MEAN DIFFERENCE BETWEEN NUMBER OF CIGARETTES SMOKED PER DAY IN 1973–1980 AND IN 1963–1972, BY CASE–CONTROL STATUS, AND BY TAR LEVEL IN 1973–1980[a,b]

	Tar level, 1973–1980, mg/cigarette				
	≤14.0	14.1–17.5	17.6–21.0	21.1–28.0	All
Cases	+6.8* (25)	+2.1 (130)	+0.7 (78)	0.0 (139)	+1.4 (372)
Controls	−1.1 (27)	+0.8 (89)	+1.3 (45)	−0.1 (83)	+0.4 (244)

[a] Difference = No. cigs/days (1973–1980) − No. cigs/day (1963–1972). No. of subjects in parentheses.

[b] Total No. of subjects = 616; 4 subjects who smoked throughout 1973–1980 did not smoke throughout 1963–1972.

* $P < 0.05$ for difference in mean difference between cases and controls.

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associate ourselves in this study, is to derive a scale from cigarette tar-content information. Although some controversy surrounds the Federal Trade Commission's methods and published lists of smoke component measures, the ordering of particular brands with respect to others is likely to be correct, and *per extenso* the allocation of smokers into average tar level groups.

There are only a few studies that address the question of lower risk from lower tar by investigating *exclusive* users of either low- or high-tar cigarettes (more usually, lifelong filter vs plain tip). In the age groups of high lung cancer incidence, it is not easy to accumulate numbers of smokers of "pure" type, who have never changed from plain to filter tip. Vutuc and Kunze (2[illegible]) reported a risk reduction of 59% for their middle tar-content category (corresponding roughly to our two middle tar-level groups, combined), compared with their high one (corresponding to our highest tar-level group), with adjustment for age, duration, and intensity of smoking. The authors have included former smokers in their sample without adjusting for cessation: this complicates the issue since if smokers stopped a number of years ago, then they could not have been smoking the lower-tar cigarettes; on the other hand, even short periods of cessation may far outweigh the effect of tar reduction.

The parent data set of which the Vutuc and Kunze sample comprises a subset has been more extensively analyzed by Lubin and co-workers (12). Much of this work addressed filter/nonfilter differences, with attendant definitional difficulties. Restricting themselves to smokers never quitting, they found the equivalent of a 56% reduction in risk for those who smoked only filter cigarettes compared with those who smoked only non-filters, adjusted for duration of smoking; they stated that there was little change after adjustment for age or intensity.

While studies such as the two above offer a sense of methodological purity in their effort to compare undiluted types (lifelong "low-tar," "filter," "high-tar," or "plain"), they are difficult to interpret because populations of lifetime filter-only (low-tar) smokers differ sharply from plain-only (high-tar) smokers. Specifically, among our control smokers (subset B, Table 1), the 11 lifelong filter smokers were significantly different from the 77 lifelong non-filter smokers in the respect that they averaged 10 years younger, started smoking 5 years later, smoked almost a half a pack less per day, and overall had one-third the total packyears exposure. These results are similar to those found in a large series of smoking histories recently assembled by Wynder *et al.* (27). Clearly, behavioral aspects of smoking and age of the smoker need to be controlled carefully, especially in any comparison of users of exclusively one type of cigarette with another type.

The majority of studies on lung cancer risk in relation to tar content have, as in our study, attempted to quantify an hypothesized decreased risk among persons presently smoking low-tar (or filter) cigarettes, after some term of smoking higher tar (or nonfilter) cigarettes. Some of this work suggested a substantial risk reduction. Bross and Gibson (2) examined filter vs non-filter cigarette users as defined by the type currently used. Filter users showed a risk reduction of 44% with adjustment for both duration and intensity of smoking; age was not controlled in the analysis, although the entire study sample of controls was age-matched to the

cases. Wynder *et al.* (28), who likewise age-matched and adjusted for intensity, found a risk reduction of 41% for their subjects who smoked filters for at least 10 years, relative to plain-tip smokers.

Other studies have suggested a smaller reduction in risk. Wynder and Stellman (30) again compared long-term filter smokers with non-filter users, but adjusted simultaneously for intensity and either age or duration; the reduction for the former group was either 16 or 21%, respectively. Likewise, Hammond *et al.*'s prospective study (8), matching subjects on an extensive variable list, yielded almost identical figures for risk reduction of lung cancer among smokers of low-tar vs high-tar cigarettes, 17% for the 1960–1966 part of the study, 21% for the 1966–1972 part. Lubin *et al.* compared long-term low-tar brand users with long-term high-tar brand users, and found a risk reduction of about 30% (13). This analysis was controlled for number of cigarettes, length of habit, and cessation; the cases and controls being originally age-matched, apparently no adjustment for age was done.

In our study, examination of smoking histories and the distribution of average tar levels convinced us that the defined groups reflect real classes of behavior, especially in 1973–1980: persons in the highest reference group still smoked non-filter cigarettes; the majority, in the two middle groups of the distribution, were smokers of popular and long-established (but changing over time) brands of filter cigarettes; those in the lowest group changed to the lowest-tar cigarettes available.

The initial unadjusted result of Table 2 indicated a risk reduction of half for persons smoking a cigarette in the 14 mg or lower tar range. However, any adjustment for lifetime smoking rendered the apparent risk reduction nonsignificant. Inclusion of other confounders such as age decreased the risk reduction further, to only 17% for the lowest-tar group, a point at which it can hardly even be characterized as nonsignificant but suggestive. As Doll and Peto (3) have concluded, smokers in the age groups that contribute the great bulk of lung cancer cases appear to have been in fact so early and so intensely exposed to tobacco smoke that the only form of tar reduction that gives any significant benefit to them is complete cessation. Kunze and Vutuc (10) arrrived at much the same conclusion.

One simple explanation for our observed absence of significant risk reduction could be that the theoretical benefit of reduction of intake of proven harmful material per cigarette smoked is offset by smoking more cigarettes. Other investigators have surmised variously, for smokers switching to lower-tar cigarettes, that there is no compensatory increase (6, 29), that there might be a small increase (9, 11), that there certainly is an increase (17, 27), or that their data are inappropriate for the question (26); the Surgeon General urges further research (24). Our data indicate that a subgroup of smokers in this study distinctly alters its behavior in such a way as to diminish the putative benefit: cases who smoked cigarettes with the lowest available tar for nearly 20 years also increased the number they smoked by almost half a pack per day. However, at the risk of advancing a *post hoc propter hoc* argument, the fact that controls did not show similar compensation suggests that tar reduction could still be of some benefit.

In recent years considerable discussion has been devoted to the proposition that, since smokers are not going to quit in large numbers no matter how grim the potential health consequences, perhaps some benefit might be gained by promoting brand-switching, or by redesigning cigarettes (7, 24). The implication of our finding of demonstrated significant compensation is that public health efforts aimed at converting smokers to the use of low-tar cigarettes must simultaneously emphasize the need to avoid smoking more cigarettes. Moreover, should there still be any doubt, efforts to promote smoking cessation and to prevent smoking initiation should be emphasized and intensified however possible.

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Independence of Dysplastic Nevi from Total Nevi in Determining Risk for Nonfamilial Melanoma[1]

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In the determination of risk for melanoma, relatively little is known about the possible independence of two important predictors, total nevi and clinically dysplastic nevi. From a study conducted in Sydney, Australia [see J. J. Nordlund *et al.*, *Cancer Res.* 45, 1855–1861 (1985)], 246 cases of melanoma (excluding 7% of targeted patients with a history of melanoma in a first-degree relative) were compared with 134 nonmelanoma controls. Participants had been examined by a dermatologist and an oncologist. Logistic regression analysis was used and included an age–sex interaction term in computing all estimates of relative risk in this report. Relative risk for melanoma in those with 16+ total nevi was significantly elevated at 1.8 but declined to a statistically nonsignificant level of 1.2 (95% confidence limit (CL): 0.7, 2.0) after adjustment for dysplastic nevi. In contrast, relative risk for melanoma in those with any dysplastic nevi was 7.6 (95% CL: 3.6, 16.0) but was maintained at a similarly elevated and statistically significant level of 7.7 (95% CL: 3.5, 17.1) after adjustment for total nevi. These patterns were even more evident in the younger half of the study population. The analyses suggest that much of the association between TN and nonfamilial melanoma is explained by the presence of dysplastic nevi and, conversely, they imply that dysplastic nevi represent a clinically distinct, qualitative disorder rather than simply a quantitative disorder wherein dysplastic nevi stem merely from an increase in total nevi. The dysplastic nevus syndrome accounts for 32% of all nonfamilial melanomas.

INTRODUCTION

Two lines of research have identified nevocytic markers of risk for cutaneous malignant melanoma. This tumor has been related to a *quantitative* melanocytic change, an increase in numbers of nevi (6, 7, 10, 14). Melanoma is also associated with *qualitative* melanocytic abnormalities, the occurrence of clinically dysplastic nevi (DN) (11, 12, 14), with relative risks for melanoma of sixfold or greater. The latter work stemmed from studies in the familial setting (3, 8), studies which later suggested a 100% lifetime risk (approaching infinite relative risk) in individuals with DN who also belonged to families in which two melanomas had occurred (9).

It is clear that DN are clinically and biologically significant in these rare family kindreds. In the nonfamilial setting, however, the association of DN with melanoma, although substantial, is less strong than in the rare family kindreds reported (3, 8, 9), and for these more common melanomas, some skepticism (1) regarding

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